REMARKS

The Office Action of February 14, 2003 has been carefully reviewed. No claims are allowed. Claims 1, 3, 5-14 and 17-24 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Briefly, the present invention relates to a conjugate characterized by covalently binding at least one therapeutic agent for joint diseases, for example, matrix metalloprotease inhibitors, to hyaluronic acid, a derivative or a salt thereof, by means of a spacer.

The Examiner asserts that in the event that claim 1 is found allowable, claims 12-14 will be objected to under 37 CFR 1.75 as being substantial duplicates thereof. Claim 12 has been amended to recite "a pharmaceutically acceptable diluent" as an additional ingredient to the conjugate.

Claim 9 is rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Examiner states that claim 9 lacks positive antecedent basis for "the conjugate of the matrix metalloprotease inhibitor" and is therefore indefinite. This claim has been

amended. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1, 2, 11-14 and 17 are rejected under 35 USC 102(b) as being anticipated by Della Valle et al. The Examiner states that Della Valle et al. teach esters of hyaluronic acid with cortisone and various related derivatives, as well as methods of making them by reacting a carboxyl group of hyaluronic acid with a site on the cortisone or derivative that does not interfere with activity.

This rejection is respectfully traversed. Claim 1 has been amended to recite the limitation of "covalently binds to" and "via a spacer." Thus, it is believed the rejection is thereby obviated. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1, 2, 11-14 and 17 are rejected under 35 USC 102(b) as being anticipated by Vasilionkaitis. The Examiner states that this reference teaches a polyvinylpyrrolidone complex of hyaluronic acid, as well as a method of making said complex.

This rejection is respectfully traversed. As noted above, Claim 1 has been amended. It is believed the claim amendments obviate the rejection; reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-14 and 17-22 are rejected under 35 USC 103(a) as being unpatentable over Della Valle et al. in view of Gallardy

et al., and further in view of Falk et al. The Examiner states that it would have been obvious for a person of ordinary skill in the art at the time of the invention to make a conjugate comprising a matrix metalloprotease inhibitor and hyaluronic acid or a derivative thereof and administer it to a patient having joint disease.

This rejection is respectfully traversed. Claims 1, 8, 9, 12, 17, 20-22 have been amended. Della Valle discloses that when alcohols of aliphatic acid are therapeutically active, hyaluronic acid is merely used as a vehicle. (Col. 4, lines 45-50 and col. 10, lines 38-41). For the esters disclosed in Della Valle, the effect of the drug is exhibited only after the drug is freed from the hyaluronic acid. i.e., the hyaluronic acid is merely a carrier. (Col. 5, line 3). Because the Della Valle reference is directed towards the use of hyaluronic acid as a carrier of a prodrug, it is quite different from the present invention, in which a *synergistic* effect of a therapeutic agent and hyaluronic acid in a conjugate is seen. The synergistic effect is described in the present application, *inter alia*, on papers 8, 62, and 65. Furthermore, Della Valle neither discloses nor suggests a drug covalently bound to hyaluronic acid by means of a spacer. Therefore, the synergistic effects of the present conjugate is not rendered obvious by the teachings of Della Valle.

Gallardy relates to matrix metalloprotease inhibitors. However, Gallardy merely discloses a general description that the matrix metalloprotease inhibitors may be conjugated to carriers, without providing a specific description or example of a conjugate.

Further, Gallardy neither discloses nor suggests a covalent bond of at least one therapeutic agent for joint diseases to hyaluronic acid, a derivative or salt thereof by means of a spacer, the crux of the present invention.

Falk relates to a combination or formulation of hyaluronic acid and a drug. It discloses that hyaluronic acid acts as a carrier, so that the effect of the drug is only seen after the drug is liberated from the hyaluronic acid. Therefore, the hyaluronic acid disclosed in Falk is not bonded to a drug.

Gallardy and Falk do not satisfy the deficiencies noted for Della Valle. Because the synergistic effects of the present conjugate are neither taught nor suggested by any one or combination of the cited art, there is no *prima facie* case of obviousness under 35 USC 103. For these reasons, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1,2, 11-14 and 17-19 are rejected under 35 USC 103(a) as being unpatentable over Della Valle et al. in view of Bemis et al., and further in view of Falk et al. The Examiner states that a worker of ordinary skill in the art would have been

motivated to substitute the cyclooxygenase-2 inhibitor of Bemis for the cortisone of Della Valle because those skilled in the art at the time of the invention would have recognized that the cyclooxygenase-2 inhibitor had an appropriate site for binding to hyaluronic acid, and both cyclooxygenase-2 inhibitors and cortisone were known to be usable for the purpose of treating joint disease. This rejection is respectfully traversed. Bemis does not disclose a combination or formulation of hyaluronic acid and a drug. Bemis also does not disclose or suggest covalent binding of a drug to hyaluronic acid via a spacer. Thus, because this reference does not overcome the deficiencies of the Della Valle primary reference, there is no *prima facie* case of obviousness under 35 USC 103. For these reasons, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1,2, 11-14 and 17-19 are rejected under 35 USC 103(a) as being unpatentable over Della Valle et al. in view of Falk et al., and further in view of Wunderlich et al. The Examiner states that it would have been obvious for a person of ordinary skill in the art to make a conjugate comprising at least one therapeutic agent for joint disease which is an antirheumatic drug and hyaluronic acid or a derivative thereof and administer it to a patient having joint disease. The examiner asserts that a worker of ordinary skill in the art would have been motivated to substitute the NSAID of Falk for the cortisone of Della Valle

because those skilled in the art at the time of the invention would have recognized that the NSAID had an appropriate site for binding to hyaluronic acid, and both NSAIDs and cortisone were known to be usable for the purpose of treating joint disease. This rejection is respectfully traversed. The Wunderlich reference does not overcome the deficiencies of the other two references cited. It does not teach a combination or formulation of hyaluronic acid and a drug nor does it teach or suggest a covalent bond of a drug to hyaluronic acid by means of a spacer. Therefore, a prima facie case of obviousness cannot be sustained. Reconsideration and withdrawal of the rejection are respectfully requested.

It is thus submitted that the claims comply with 35 U.S.C. §112 and are free of the prior art. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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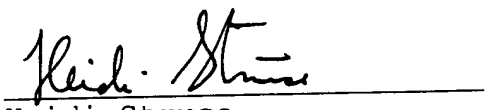
By 
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